

# Assessment of serum adiponectin and leptin levels in patients with ischaemic heart disease: an association with the ejection fraction, coronary calcium score and coronary angiogram

Ocena stężeń adiponektyny i leptyny w surowicy u pacjentów z chorobą niedokrwienną serca – związek z frakcją wyrzutową, wskaźnikiem uwapnienia tętnic i angiogramem tętnic wieńcowych

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## Abstract

**Introduction.** Adiponectin is an adipose tissue-derived adipocytokine protein, while leptin is the protein that maintains the body weight in humans via its effect on the hypothalamus. These hormones interact at different levels of cardio-metabolic risk factors.

This study aimed to assess the serum levels of adiponectin and leptin in patients with ischaemic heart disease and subjected to coronary calcium scoring (CCS) and coronary angiography.

**Material and methods.** We included 59 patients with ischaemic heart disease and 20 healthy subjects served as a control in this study. The patients were assessed by electrocardiograph, echocardiograph, coronary angiogram and coronary computerised tomography (CCT) for the assessment of CCS. Serum levels of adiponectin and leptin were determined by using enzyme-linked immunosorbent assay (ELISA) technique.

**Results.** Coronary computed tomography (CT) investigation explored, that 30.5% of patients had positive calcium score and 67.8% of patients did not show evidence of coronary changes by CT angiograph. The patients had significantly high leptin and low adiponectin levels compared with healthy subjects. Serum leptin levels were significantly low in patients with positive CCS and angiogram, compared with those who had no abnormal CCT. Significant positive correlation between ejection fraction and serum leptin ( $r = 0.285$ ,  $p < 0.05$ ) and non-significant correlation with serum adiponectin were observed.

**Conclusions.** Serum leptin and adiponectin levels are useful determinants in patients with ischaemic heart disease, as high serum leptin levels are associated with negative coronary CT and positively correlated with left ventricular ejection fraction.

Key words: leptin, adiponectin, coronary calcium score

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## Introduction

Adiponectin is an adipose tissue-derived adipocytokine protein. In the circulation, adiponectin is available as a low-molecular-weight trimer, medium-molecular-weight hexamer, and a high-molecular-weight multimer form [1], that has stronger anti-atherogenic effects than other types of adiponectin [2]. Adiponectin is an important mediator against the development of coronary atherosclerosis [3, 4] and a low adiponectin level is a risk factor for cardiovascular events [5]. Low level of adiponectin concentration is observed in patients with coronary artery disease [6], or its risk factors [7] and it is also independently associated with the development of coronary artery calcification (CAC) [8]. The anti-atherosclerotic effects of adiponectin are achieved through improving the endothelial function and repair by endothelial progenitor cells; inhibiting the neointimal formation by suppressing proliferation and migration of vascular smooth muscle cells [9, 10] and blocking inflammation and foam cell formation from macrophages [11].

Leptin is a protein that plays a role in maintaining the body weight in humans via its effect on the hypothalamus. Leptin is involved in the regulation of the myocardial blood flow via its effect upon the vasoreactivity of coronary blood vessels [12] in addition to the prothrombotic effect [13]. The literature review revealed conflicting results about the association of coronary artery disease with leptin. Some authors reported an association between leptin with increased risk of the incident CAD [14, 15], while others found no association [16]. Khafaji et al. [17] found, that serum leptin levels increased after myocardial infarction and may be predictors of the left ventricular ejection fraction and the degree of atherosclerosis. Martin et al. [18] found, that serum leptin levels increased in asymptomatic overweight-obese individuals and were independently associated with increased coronary calcium score in the presence of high C-reactive protein levels. This study aimed to assess the association between hormones (notably adiponectin and leptin) that play a role in controlling the energy homeostasis and coronary artery atherosclerosis assessed by different diagnostic modalities, including coronary calcium scoring and coronary angiography.

## Material and methods

This study was conducted in the Department of Medicine, College of Medicine, Diyala University in Iraq. Each patient signed a consent form prior to the admission to the study. The study was conducted according to the ethical guidelines constructed by the Scientific Committee of the Institute, in which the treatment or using device should not be harmful to the patient and the patient is free to decline from the study or to refuse for study admission.

The authors recruited the patients from the Consultant Clinics at The General Teaching Hospital of the College of Medicine in Diyala, Iraq. The patients had a previous history of coronary artery disease (including old myocardial infarction, and stable angina pectoris), and newly diagnosed coronary artery disease presented with chest pain on exertion, breathlessness, palpitation, etc. The criteria of exclusion included patients with a history of secondary hypertension, diabetes mellitus, chronic liver diseases, renal disorders, autoimmune diseases and drug intake e.g. non-steroidal anti-inflammatory drugs.

This study included 59 patients (24 men and 35 women) with clinical symptoms of ischaemic heart disease (frequent chest pain, dyspnea and palpitation). Another 20 healthy subjects served as a control were enrolled for determining the baseline levels of adiponectin and leptin and using these values as baseline data for the comparison with the values of patients. All healthy subjects had normal ECGs records without any evidence of ischaemic heart disease or arrhythmias, normal blood pressures (the systolic and diastolic blood pressures were less than 140 and 80 mm Hg) and the fasting lipid profiles were within normal limits. Demographic data, medical history and treatment were obtained from each patient. Modifiable risk factors, events or complications, and current therapy were recorded. A person who reported smoking on admission was assigned as current smoker. The anthropometric measurements, including height (m), weight (kg), waist circumference (cm) and hip circumference were measured. The body mass index (BMI), waist/hip ratio waist/height ratios were calculated. The cut-off values for cardiometabolic risk factors were: BMI  $\geq 25$  kg/m<sup>2</sup>, waist circumference  $\geq 102$  cm and waist to height ratio  $> 0.5$ .

The blood pressure (mm Hg) was measured in sitting position, and the mean of three readings was taken. The difference between systolic and diastolic blood pressure represented the pulse pressure and the mean arterial blood pressure was equal to diastolic blood pressure + 1/3 pulse pressure. Systolic and diastolic blood pressures if  $\geq 140$  and 90 mm Hg respectively were considered as high blood pressure, whether the patients were treated or not with antihypertensive drugs. Then each patient was assessed by the electrocardiograph, echocardiograph, coronary angiogram and coronary computed tomography (coronary CT) for assessing coronary artery calcium score. In respect to the medical ethics, coronary angiogram and CT were not done.

Peripheral venous blood samples were drawn immediately into tubes on the day of the admission, then the blood samples were centrifuged at 2500 rpm for 10 minutes, and the sera were separated for determination of fasting lipid profile, and adiponectin and liponectin.

The determinants of lipid profile included fasting serum total cholesterol (TC), triglycerides (TG) and high-density

lipoprotein-cholesterol (HDL-c). The LDL-c lipoprotein (low-density lipoprotein-cholesterol, LDL-c) is determined by using the equation: TC- (HDL-c + TG/5). The log of the ratio of the triglyceride to the high-density lipoprotein value is the atherogenic index. Cut-off values of fasting serum triglyceride if  $\geq 150$  mg/dL and high-density lipoprotein  $\leq 35$  mg/dL (men) and 50 mg/dL (women) were considered as cardiometabolic risk factors.

Quantitative determination of serum adiponectin and leptin was determined by using the enzyme-linked immunosorbent assay (ELISA) technique. The principles of these tests are these substances reacted with polyclonal anti-human adiponectin or leptin antibody in a conjugation with a horseradish peroxidase enzyme in a microtitre plate well.

### Statistical analysis

Data are expressed as number, percent, mean  $\pm$  standard deviation (SD). Unpaired and paired Student's t-test was used to evaluate differences between the two groups. For all the tests, a two-tailed  $p \leq 0.05$  was considered statistically significant. All calculations were made using Excel 2003 program for Windows.

### Results

Table 1 shows the characteristics of patients with ischaemic heart disease enrolled in this study. The mean age was 56.7 years. About one-third of patients have a previous ischaemic heart disease.

The current ECG findings of myocardial ischaemia were present in 44.1% of the patients (Table 1). Left ventricle hypokinesia and left ventricular hypertrophy were observed in 10.1% (Table 1). Coronary CT investigation explored, that 30.5% of patients had a positive calcium

**Table 1.** Characteristics of the study

Variables	Values
Gender (male:female)	24:35
Age (years)	56.7 $\pm$ 8.0
Previous history of ischaemic heart disease	18 (30.5)
ECG findings (ischaemia) (positive)	26 (44.1)
Echocardiograph findings:	
• ejection fraction	69.5 $\pm$ 3.3
• hypokinesia of left ventricle	6 (10.2)
• left ventricular hypertrophy	6 (10.2)
Coronary computed tomography:	
• calcium coronary score (positive)	18 (30.5)
• angiography (negative)	40 (67.8)

The results expressed as a number (percentage), and mean  $\pm$  standard deviation; ECG – electrocardiograph

score and 67.8% of patients did not show evidence of coronary changes by CT angiography (Table 1). At the time of entry into the study, the means systolic and diastolic blood pressures of the patients were within the normal range (Table 2). The mean systolic and diastolic blood pressures were 136.6 and 84.7 mmHg, respectively. Systolic and diastolic blood pressure of  $\geq 140$  mm Hg and  $\geq 90$  mm Hg was observed in 29 (49.2%) and 26 (44.1%) patients respectively. The results of anthropometric measurements revealed, that the patients were overweight by the evidence of that the value of the mean body mass index was  $28.93 \pm 3.3$  kg/m<sup>2</sup> (Table 2). The waist circumference of  $\geq 102$  cm was observed in 39 (66.1%) of patients and the mean value was 103.1 cm. The mean waist/hip and waist to height ratios exceeded normal limits, and their means were 0.98 and 0.627 respectively (Table 2). The mean value of fasting serum triglyceride was 180 mg/dL, which is higher than the critical level of 150 mg/dL. Fifty-six of the patients had a serum triglyceride level above 150 mg/dL. The mean value of serum high-density lipoprotein was 46.8 mg/dL; 24 out

**Table 2.** Cardio-metabolic risk factors

Variables	Determinant values
<b>Blood pressure measurement [mm Hg]</b>	
Systolic	136.6 $\pm$ 16.6
Diastolic	84.7 $\pm$ 7.6
Pulse pressure	51.9 $\pm$ 10.7
Mean arterial	102 $\pm$ 10.2
<b>Anthropometric measurements</b>	
Body mass index [kg/m <sup>2</sup> ]	28.93 $\pm$ 3.3
• < 25	7 (11.9)
• $\geq 25$	52 (88.1)
Waist [cm]	103.13 $\pm$ 7.63
• $\geq 102$	39 (66.1)
Hip [cm]	105.4 $\pm$ 8.64
Waist/hip ratio	0.98 $\pm$ 0.046
Waist/height ratio	0.627 $\pm$ 0.037
<b>Fasting serum lipid profile [mg/dL]</b>	
Triglycerides [mg/dL]	180.6 $\pm$ 33.9
• $\geq 150$	56 (94.9)
Cholesterol [mg/dL]	182.1 $\pm$ 36.8
High-density lipoprotein [mg/dL]	46.8 $\pm$ 5.5
• $\leq 35$ (men) or $\leq 50$ (women)	24 (40.7)
Low-density lipoprotein [mg/dL]	99.2 $\pm$ 36.9
Very-low-density lipoprotein [mg/dL]	36.1 $\pm$ 6.8
Atherogenic index	0.583 $\pm$ 0.102

The results expressed as mean  $\pm$  standard deviation and number (percentage)

**Table 3.** The results of coronary calcium score and angiogram

Variables	Measurements
<b>Calcium score (Agatstone)</b>	
No score	41 (69.5)
1-50	4 (6.8)
51-100	5 (8.5)
101-200	1 (1.7)
201-300	1 (1.7)
> 301	7 (11.9)
<b>CT angiogram (critical lesion)</b>	
One vessel	
Left anterior descending	11 (18.6)
Left circumflex	2 (3.4)
Right	1 (1.7)
Two vessels	4 (6.8)
Three vessels	1 (1.7)

The results expressed as a number (percentage)

of 35 women had a level  $\leq 50$  mg/dL. The atherogenic index, that represents the log (triglyceride/high-density lipoprotein ratio) was higher than the cut-off ratio and was equal to 0.583. The data of coronary CT revealed, that there is a variation in calcium score, and seven patients had a calcium score ranged between 372–595 Agatstone (Table 3). Eleven patients had a critical lesion in the left anterior descending coronary artery with a positive CT angiogram. Five patients with critical lesions in coronary arteries had a negative result of calcium score, that is, zero. The serum leptin levels of the patients were significantly higher ( $p < 0.001$ ) than healthy subjects ( $1329.9 \pm 754.5$  ng/mL vs  $140.2 \pm 26.2$  ng/mL, respectively), while the serum adiponectin levels were significantly ( $p < 0.001$ ) less than corresponding levels of healthy controls ( $0.039 \pm 0.030$  ng/ml vs  $0.2 \pm 0.01$  ng/mL, respectively) (Table 4). The serum leptin levels were significantly low in patients with a positive calcium score and angiogram coronary CT, compared with those who had no abnormalities in coronary CT. Further analysis revealed a significant positive correlation between body mass index with serum leptin ( $r = 0.296$ ,  $p < 0.02$ ), and non-significant negative correlation with adiponectin ( $r = -0.1$ ,  $p > 0.05$ ). An inverse significant correlation was found between the log atherogenic index with serum leptin ( $r = -0.354$ ,  $p < 0.01$ ), but it did not correlate with serum adiponectin. Moreover, a significant positive correlation between ejection fraction percentage with serum leptin ( $r = 0.285$ ,  $p < 0.05$ ), and a non-significant correlation with serum adiponectin ( $r = 0.155$ ,  $p > 0.05$ ) were observed.

**Table 4.** Serum levels of leptin and adiponectin

Variables	Serum adiponectin [ng/mL]	Serum leptin [ng/mL]
Minimum–maximum	34.4–2625.3	0–0.164
Median	1329.9	0.031
Mean $\pm$ SD	$1329.9 \pm 754.5$	$0.039 \pm 0.030$
<b>Coronary CT</b>		
Negative calcium score	$1630 \pm 639.6$	$0.041 \pm 0.027$
Positive calcium score	$670.8 \pm 626.9^*$	$0.037 \pm 0.037$
<b>Coronary angiogram</b>		
Negative angiogram	$1786.9 \pm 523.3$	$0.038 \pm 0.028$
Positive angiogram	$443.5 \pm 255.8^*$	$0.041 \pm 0.035$

The results are expressed as mean  $\pm$  standard deviation (SD); \*compared with corresponding negative data; CT – computed tomography

## Discussion

The results of this study showed significant paradoxical alterations of serum leptin levels, and non-significant changes in serum adiponectin levels in patients with ischaemic heart disease. Cardio-metabolic risk factors in terms of overweight-obesity and abnormal lipid profile (high fasting serum triglycerides and low high-density lipoprotein) were detected in considerable percent and in agreement with other studies [19, 20]. The data of coronary calcium score revealed, that 18 patients were at risk of future myocardial infarction. Yamamoto et al. [21] reported, that the cardiovascular disease mortality is significantly higher among patients who had a CAC score  $\geq 100$  than among those with a CAC score  $< 100$ , that means nine patients of our study were at high risk. The mean values of blood pressure measurement were within the normal values and possibly not influenced the present results with adiponectin and leptin as dysregulation of adipokines levels is associated with resistant hypertension [22]. The pattern of the atherogenic lipid profile is commonly observed in patients with coronary artery disease. High percentage of patients are obese, and they are at risk of cardiovascular disease, therefore, obesity may influence the adipokines levels, as the serum leptin levels are increased while adiponectin levels are decreased in obesity [23, 24]. Significant positive correlation between serum leptin levels and BMI highlights the importance of serum leptin levels as an indicator of cardio-metabolic risk factors. In addition, low serum leptin levels in patients with negative coronary CT compared with those with positive data indicated, that leptin *per se* is not involved in coronary atherosclerosis or in the plaque instability [25]. The non-significant inverse correlation between serum adiponectin levels and body mass index besides the non-significant differences in adiponectin levels between

patients with positive and negative CT do not agree with another study, that demonstrated that low levels of total or high-molecular-weight adiponectin levels are associated with the calcified or non-calcified coronary plaque [26]. The other important result is the significant correlation between serum leptin levels and the left ventricular ejection fraction, that indicated the serum leptin might serve as a predictor of cardiac function [17]. Therefore, this study is an attempt to provide further data in the above topic and is worth attention.

## Conclusions

We conclude, that high serum leptin levels impact a favourable effect upon the patients with ischaemic heart disease, as it was associated with negative coronary CT and improvement in left ventricular function.

## Conflict of interest(s)

The authors declare no conflict of interest.

## Streszczenie

**Wstęp.** Adiponektyna jest adipocytokiną, białkiem produkowanym przez tkankę tłuszczową, natomiast leptyna jest białkiem przyczyniającym się u ludzi do utrzymania masy ciała przez wpływ na przysadkę mózgową. Hormony te oddziałują na siebie na różnych poziomach czynników ryzyka sercowo-naczyniowego. Badanie przeprowadzono w celu oceny stężeń adiponektyny i leptyny w surowicy pacjentów z niedokrwinną chorobą serca, których poddano koronarografii i u których określono wskaźnik uwapnienia tętnic (CCS).

**Material i metody.** Do badania włączono 59 pacjentów z chorobą niedokrwinną serca i 20 zdrowych osób tworzących grupę kontrolną. U chorych wykonano badania elektrokardiograficzne, echokardiograficzne, koronarografię i tomografię tętnic wieńcowych (CCT) w celu oceny CCS. Surowicze stężenia adiponektyny i leptyny oznaczono metodą immunoenzymatyczną (ELISA).

**Wyniki.** W ocenie uwapnienia tętnic, dokonanej za pomocą tomografii komputerowej (CT) tętnic wieńcowych, u 30,5% chorych uzyskano wynik dodatni, a u 67,8% chorych nie stwierdzono zmian w tętnicach wieńcowych w angiografii CT. U osób z chorobą niedokrwinną stężenia leptyny były istotnie wyższe, a adiponektyny – niższe niż w grupie kontrolnej. U chorych z dodatnim CCS i zmianami w angiogramie stężenie leptyny w surowicy było istotnie niższe niż u osób bez nieprawidłowości w CCT. Stwierdzono istotną dodatnią korelację frakcji wyrzutowej ze stężeniem leptyny w surowicy ( $r = 0,285$ ;  $p < 0,05$ ) oraz nieistotną korelację ze stężeniem adiponektyny w surowicy.

**Wnioski.** Surowicze stężenia leptyny i adiponektyny są użytecznymi wskaźnikami u pacjentów z chorobą niedokrwinną serca, ponieważ wysokie stężenie leptyny wiązało się z ujemnym wynikiem CCT i korelowało dodatnio z frakcją wyrzutową lewej komory.

Słowa kluczowe: leptyna, adiponektyna, wskaźnik uwapnienia tętnic wieńcowych

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